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Blood Glucose Levels in Portal and Peripheral Circulation and Their Relation to Food Intake in the Rat

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STRUBBE, J. H. AND A. B. STEFFENS. *Blood glucose levels in portal and peripheral circulation and their relation to food intake in the rat.* *PHYSIOL. BEHAV.* 19(2) 303–307, 1977. – Rats weighing about 450 g were provided with permanent catheters in the portal vein and the right auricle. This method allows blood sampling from the portal and peripheral circulation at the same moment in the nondisturbed unanesthetized rat. In the ad lib condition the portal glucose level was higher than that in the general circulation before, during, and after the meal. After a fast of 22 hr premeal portal vein levels were equal to those of the general circulation. During the meal the portal glucose levels rose to about 150 mg per 100 ml whereas those of the general circulation did not exceed 130 mg/100 ml. Experiments with glucose infusions systemically and intraportally show that, under conditions of mild deprivation, the level of glucose in the portal vein plays no or only a very minor role in the termination of feeding.

Blood glucose Food intake Portal vein

AFTER absorption from the intestines glucose is transported via superior and inferior pancreaticoduodenal vein, gastroduodenal vein, and several mesenteric veins to the main stream of the portal vein [2]. The blood of the portal vein flows through the liver where part of the glucose is absorbed. As the liver is the first organ through which the glucose flows it might play an important role in the regulation of food intake by signalling the amount of carbohydrate ingested. Evidence for such an involvement of the liver is presented by several authors [6, 7, 8, 9, 10, 11]. In particular, Russek demonstrated that portal infusion of large doses of glucose in the dog causes premature termination of an ongoing meal [7]. It therefore seems possible that termination of meals is under glucostatic control.

To put this hypothesis to a further experimental test an attempt was made to inhibit food intake in deprived rats by increasing the portal glucose concentration to high levels by means of continuous intracardial or intraportal infusion of glucose (Experiment 1). No inhibition was seen, but this alone was an insufficient basis for any conclusion as to the role of liver glucoreceptors in the control of food intake until it was shown that the glucose levels in the portal vein during infusion exceeded those during food intake (Experiment 2).

METHOD

Animals and Maintenance

Male Wistar rats were maintained in individual perspex chambers (25 × 25 × 30 cm) at a room temperature of

20°C. Lights were on from 6 a.m. till 6 p.m. Water was allowed ad lib at all times.

A standard diet providing 20% protein, 53.5% carbohydrate, 4.5% fat, and 22% water, with added minerals and vitamins was available ad lib except during food deprivation experiments. This diet was presented in the form of a bar which could slide easily through a dispensing tube attached to one of the walls of the cage. The bar could be removed from the dispenser after a meal and weighed without disturbing the animal. Practically no food was spilled. Experiments were made during day at about 10 a.m.

After surgery rats were not used until they proved to be influenced neither by the presence of an experimenter nor by his movements during blood sampling or infusion. It often took subjects a habituation period of about one week to reach this state. The experiments were performed while the animals remained in their living cages.

Blood Sampling and Infusion Techniques

To solve the problems stated in the introduction techniques are required that do not disturb the animals. Therefore cannulas were inserted into the heart of the animals through the jugular vein using the technique described by Steffens [12]. The swivel joint of Epstein and Teitelbaum [3] used by Steffens [12] was replaced by a very small swivel joint [13]. When systemic infusions were performed the animals were provided with a double heart catheter [12], allowing continuous intravenous infusions and blood sampling from the freely moving unanesthetized animals. However, the method of Steffens was somewhat

modified. The infusion cannula ended 3 mm downstream from the tip of the sampling cannula in order to minimize the risk of contamination of the blood sample with the infusion fluid.

During repeated sampling (sample volume was 0.1 ml), stress on the rat due to loss of blood should be avoided. Therefore fresh citrated blood taken from a donor rat by heart puncture and warmed to 39°C during 5 min, was transfused after each sample. During ad lib experiments donor blood of ad lib fed animals was used whereas during experiments with fasted animals blood of fasted animals was used.

Portal Vein Cannulation

Rats were anesthetized with ether. The hairs at the place of laparotomy, just right of the processus xiphoideus, were removed and the skin was sterilized with chlorhexidine 2%. A midline incision of about 1 1/2 to 2 cm was made. The caudal liver lobes were pushed in the caudal, and the rostral lobes in the rostral direction revealing the portal vein branches to the rostral liver lobes. The branch to the right lobe was taken for cannulation. The bile duct and the hepatic artery branch were carefully separated from the portal vein branch. The latter branch was cannulated in the manner described by Steffens [12] for heart cannulation but with a silicon catheter of ID 0.3 mm, OD 0.64 mm, 15 cm long. The tip of this cannula was pushed 1 cm in the caudal direction, so that it was situated between the liver and the superior pancreaticoduodenal vein in the main stream of the portal vein. The cannula was drawn under the skin to the skull where it was attached as described by Steffens for the infusion cannula [12]. The cannula was filled with 50% polyvinyl pyrrolidone in a heparin solution of 500 U/ml.

Besides the portal cannula a heart catheter [12] was inserted. Sampling began 1 week after surgery. Blood was sampled in the day time about 4 hr after light went on.

Chemical Determinations

Blood glucose was measured with the ferri-cyanide method of Hoffman in a Technicon Autoanalyzer on samples of 0.05 ml whole blood.

Experiment 1: Effect of Infusions on Feeding Behaviour

In these experiments the rats, provided with the required sampling and infusion catheters, were fasted during 22 hr. After this fast the food was returned, and the rat began to eat almost at once. One min after the start of this meal, infusion of a 10% glucose solution was begun at a rate depending on the type of experiment, and continued during 30 min. In control experiments 0.2 ml/min saline was infused. Each rat was tested once in each condition used: the order in which conditions were presented was random. Meal size (g) and duration (min) were recorded.

Experiment 1a, Intracardial infusion. Five rats of about 350 g, provided with intracardial sampling and infusion catheters, were used. The rate of infusion was 0.083 or 0.2 ml/min (8.3 or 20 mg/min, respectively). In addition to the observations on feeding behaviour, blood samples for glucose determination were taken from the right auricle at 5, 10, 15, 20, and 25 min after meal onset.

Experiment 1b, Intraportal infusion. Six rats, body weight about 450 g, five of which had previously been used

for Experiment 3, provided with intraportal as well as double intracardial catheters, were used. The glucose solution was infused through the intraportal catheter at a rate of 0.1 ml/min (10 mg/min). Only feeding behaviour was recorded.

Experiment 2: Effects of Feeding on Blood Glucose Levels

In this experiment the rats were always provided with intraportal and intracardial catheters. The influence of a meal starting at time zero, upon systemic and/or intraportal blood glucose concentrations were studied in rats previously deprived of food for 22 or 2 hr. The 2 hr deprivation was considered sufficiently similar to the ad lib condition, but has the advantage that it ensured that the rat would take a meal during the observation. In all cases the start of the meal is termed time 0. Blood samples from the right auricle and the portal vein were always drawn at the same moment.

Experiment 2a, Ad lib 2 hr deprived. Eight rats, body weight 400–450 g were used. Samples were taken at -20, -10, 0, 5, 10, 15, 20 min in all rats and in addition at 30, 40, 50, 60, 70, 80, 90 min in five animals.

Experiment 2b, Intracardial infusion, 22 hr deprived. Five animals, body weight 450 g, were used. Samples were taken in all animals at -20, -10, -5, 0, 5, 10, and 15 min and in four of the five also at 20, 25, 30, 40, 50, and 60 min.

For reasons to be discussed below, Experiment 3 was included.

Experiment 3: Intracardial Glucose Infusion, 22 hr Deprived

Five rats, body weight 450 g, were used. The rate of infusion was 0.2 ml/min (20 mg/min). Samples were taken from the general and portal circulation at 5, 10, 15, 20 and 25 min after meal onset.

RESULTS

Experiment 1

It can be seen from Tables 1 and 2 that neither meal duration nor meal size was significantly influenced by the glucose infusions administered as compared with saline infusion, irrespective of whether the glucose was infused intracardially or intraportally.

Experiment 1

Blood glucose concentrations. The influence of intracardial glucose infusion on the time course of glucose levels in general circulation during a meal is presented in Fig. 1. For the sake of comparison, the time course of GC glucose levels during a meal with saline infusion is included in this figure. Even at the lower infusion rate (8.3 mg/min) GC glucose rises far higher than during the saline infusion, but especially at the higher infusion rate (20 mg/min) excessive hyperglycaemia is rapidly induced in the GC.

Experiment 2

a. Blood glucose concentrations. As regards the portal circulation (PC) it should be emphasized that portal glucose levels are higher than in the GC before ($p < 0.05$) and during ($p < 0.05$) the meal, and also during most of the period after the meal (Fig. 2).

b. Blood glucose concentrations. The main difference

TABLE 1

EFFECT OF INTRACARDIAL GLUCOSE INFUSION ON FEEDING BEHAVIOR

	Meal Duration (min)	Meal Size (g)
Saline infusion 0.2 ml/min	21 \pm 0.9	6.4 \pm 0.4
Glucose infusion 8.3 mg/min	19.8 \pm 1.6	5.7 \pm 0.7
Glucose infusion 20 mg/min	19.4 \pm 2.3	6.7 \pm 1.1

TABLE 2

EFFECT OF INTRAPORTAL GLUCOSE INFUSION ON FEEDING BEHAVIOR

	Meal Duration (min)	Meal Size (g)
Glucose infusion (10 mg/min)	20.1 \pm 2.7	8.4 \pm 1.3
Saline infusion (0.1 ml/min)	19.7 \pm 1.6	8.2 \pm 0.9

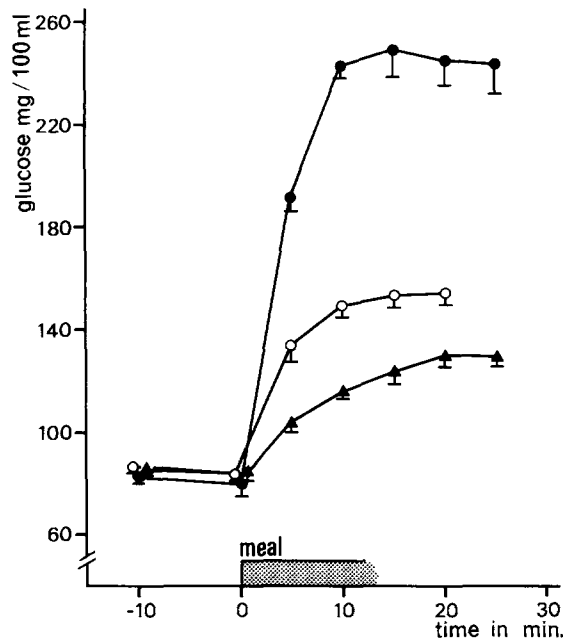


FIG. 1. Effect of intracardial glucose infusion on the glucose levels in the general circulation, during meal intake after a fast of 22 hr. For meal size and duration, see Table 1. ●—● glucose 20 mg/min, 0.2 ml/min ○—○ glucose 8.3 mg/min, 0.083 ml/min ▲—▲ saline 0.9% NaCl, 0.2 ml/min.

with Experiment 2a is that before the meal glucose levels in PC and GC are the same. After meal onset, PC levels are significantly ($p < 0.05$) higher than those in GC at 10, 15, 20, 25, and 30 min (Fig. 3).

Experiment 3

Figure 4 shows that, as was to be expected, upon intracardial glucose infusion in 22 hr deprived rats the glucose level in the PC, which before the meal did not differ from that in the GC, rises significantly ($p < 0.05$) higher than systemic concentration at 15 and 25 min. At sample times 5, 10, and 20 min the PC glucose level was not significantly higher ($0.05 < p < 0.01$).

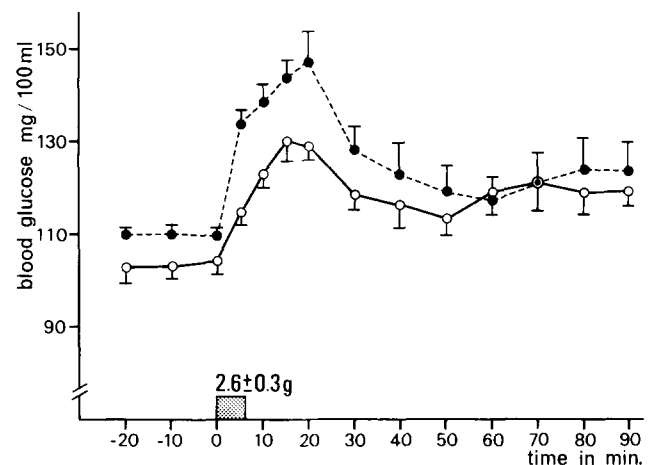


FIG. 2. Glucose levels in the portal vein ●—● and in the general circulation ○—○ in the ad lib situation.

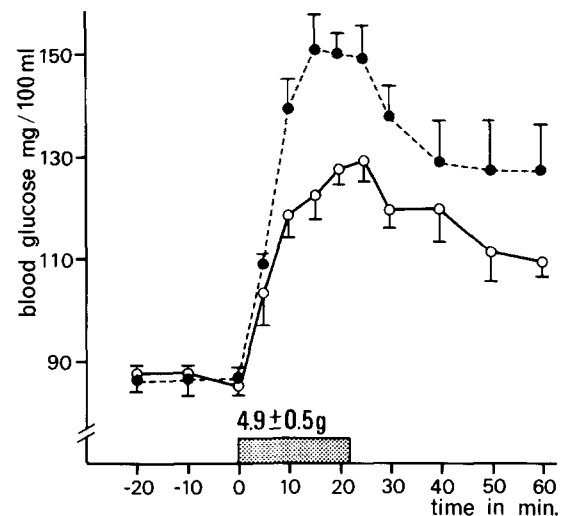


FIG. 3. Glucose levels in the portal vein ●—● and in the general circulation ○—○ after a fast of 22 hr.

DISCUSSION

Russek showed that deprived (22 hr) dogs, after return-

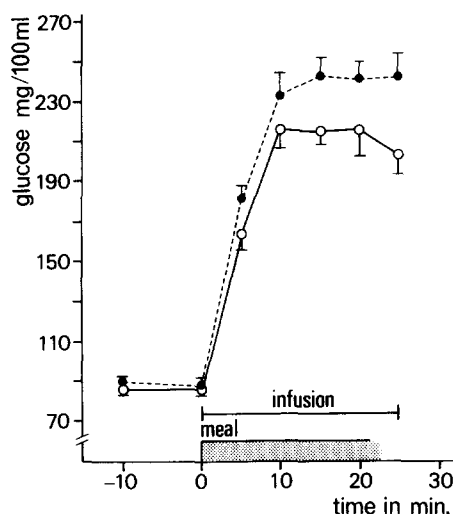


FIG. 4. Effect of glucose infusion on the glucose levels in portal vein —●—●— and general circulation ○—○— after a fast of 22 hr.

ing the food, stopped eating as soon as large loads of glucose (3–12 g) were rapidly (1–4 min) injected into the portal vein [7]. The same loads given in the general circulation did not produce inhibition of feeding. In the case of portal injection, the first passage of the glucose load through the liver will cause strong hyperglycaemia in this organ. In the case of systemic injection the load is diluted before reaching the liver and hyperglycaemia will be much milder there. This behavioural finding therefore can be plausibly explained by the assumption that hepatic glucoreceptors, which will be stimulated more strongly in the case of intraportal injection, can inhibit feeding behaviour.

Our results present that although glucose in the general circulation in the rats was increased by intracardial infusion to very high levels, there was no significant reduction of either the amount ingested or the duration of the meal.

Checking portal glucose levels during the highest infusion rate and together with food intake, revealed that these levels rose even higher than those of the general circulation (Experiment 3, Fig. 4). The latter findings were in agreement with those of Michaelis *et al.*, in which (in humans) very minor differences were observed between GC and PC glucose levels after infusion of glucose in the GC [4]. Although these high levels of glucose in the PC did not stop or inhibit feeding behaviour it might be possible that the systemic infusion of glucose in the rat did not raise portal glucose levels sufficiently.

However, the results of Experiment 2, which agree with similar data recently obtained by Anderson in the pig, refute this possibility [1] then, portal glucose either in the

ad lib condition or upon refeeding after deprivation never exceeds 150 mg/100 ml.

Comparison of the findings of Experiment 2 with the GC samples taken in Experiment 1 shows that infusion of 8.3 mg/min results in a GC glucose level which is almost identical to the level observed at the end of the meal in the PC without infusion. During infusion of 20 mg/min vastly higher GC glucose levels are attained long before the meal stops. The levels in the portal vein during the latter infusion were somewhat higher than those in the GC (see Experiment 3 and Fig. 4).

In summary, the portal glucose levels during infusion will equal or surpass (depending on the infusion rate) those occurring in normal food intake. These high levels are attained much earlier under infusion than is the case with normal meals. Yet the infusions do not affect either size or duration of the meal. Even a relatively high rate of glucose infusion into the portal vein could not prevent or inhibit the amount ingested or duration of the meal (see Table 2). It is concluded, therefore, that the glucose levels in the portal vein do not play an important role in the termination of food intake after 22 hr of deprivation in the rat.

This of course does not deny that there is some evidence that glucoreceptors are situated in the liver or portal vein. Nijima, using an isolated perfused liver-vagus preparation, recorded tonic afferent discharges with a frequency that was inversely related to the glucose concentration in the perfusion fluid [5]. In part of these experiments the glucose concentration was within the physiological range. Control experiments indicate that the effect is specific for glucose. One may speculate that these discharges would increase appetite and the lack of them would produce satiety. Schmitt showed changes (either increase or decrease) in firing rate of certain lateral hypothalamic neurons after injection of hypertonic NaCl or glucose in the portal vein of the rat, whereas no responses to such injections were found in the ventromedial, paraventricular or supra-optic nuclei [11]. These data provide at least some basis for the view that the liver contains glucoreceptors which send their signals to the hypothalamic feeding centers. However, the evidence does not clearly show whether these receptors play a role in the regulation of food intake under normal circumstances. The present infusion experiments indicate that, at least in the rat, termination of meals after deprivation is not under control of the glucoreceptors in the liver that measure the glucose concentration in the portal vein.

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